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| EXAMINER | |
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| WOODWARD, CHERIE MICHELLE | |

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| SHORTENED STATUTORY PERIOD OF RESPONSE | MAIL DATE | DELIVERY MODE |
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

| Office Action Summary | Application No.<br>10/677,148 | Applicant(s)<br>CHAPMAN ET AL. | |
|---|---|---|---|
| | Examiner<br>Cherie M. Woodward | Art Unit<br>1647 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *08 December 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1,3,4,7-10,12-24 and 30-41* is/are pending in the application.

4a) Of the above claim(s) *37-41* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,4,7-10,12-24, and 30-36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

### *Formal Matters*

1. Applicant's Response and Amendments, filed, 8 December 2006, are acknowledged. Claims 2, 5, 6, 11, 25-29 have been cancelled by Applicant. Claims 1,3,4,7-10,12-24, and 30-41 are pending. Claims 37-41 are withdrawn from consideration as being drawn to a non-elected invention. Claims 1,3,4,7-10,12-24,and 30-36 are under examination.

### *Response to Arguments/Amendments*

### *Objections to the Specification - Withdrawn*

2. The objection to the use of the trademarks ZENAPAX (pp. 21-23, 25-26, and 28) and FUNGIZONE (p. 28) are withdrawn in light of Applicant's amendments to the specification.

### *Claim Objections/Rejections Withdrawn*

3. Rejections and Objections directed to claims 2, 5, 6, 11, and 25-29 are moot in light of Applicant's cancellation of the claims.

4. The objection of claims 17 and 30 are objected to because of the following informalities of missing articles, are withdrawn in light of Applicant's amendments.

5. The rejection of claims 1,3,4,7-10,12-24,and 30-36 a under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for human patients, does not reasonably provide enablement for patients of any other species, is withdrawn in light of Applicant's amendments.

6. The rejection of claims 15-24 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention because the phrases "a given period of time" and "a period of time" are indefinite for failing to specify the metes and bounds of the time period for administration, are withdrawn in light of Applicant's amendments.

7. The rejection of claims 30-36 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention because of the phrase "delivered each day," is withdrawn in light of Applicant's amendments.

8. The rejection of claims 1, 3, 4, and 7-9 under 35 U.S.C. 102(e) as being anticipated by Blumberg et al., (US Pregrant Application US2003/0235536 A1, published 25 December 2003, priority to 15 march 2002), is withdrawn in light of Applicant's amendments.

9. The rejection of claims 1 and 3 under 35 U.S.C. 103(a) as being unpatentable over Hausen et al., (Transplantation 2000 Feb 27 69(4):488-496), is withdrawn in light of Applicant's amendments.

10. The rejection of claims 1, 3, and 4 under 35 U.S.C. 103(a) as being unpatentable over Trimarchi et al., (Nephron 2001 Apr 87:361-364), is withdrawn in light of Applicant's amendments.

11. The rejection of claims 1, 3, and 4 under 35 U.S.C. 103(a) as being unpatentable over Bumgardner et al., (Transplantation 2001 September 15 72(5):839-845), is withdrawn in light of Applicant's amendments.

12. The rejection of claims 30-36 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention because of the phrase "prevent reactions," is withdrawn in light of Applicant's amendments.

### *Claim Objections/Rejections Maintained*

13. The objection of claim 15, because the claim is missing an article, is maintained for the reasons of record. Claim 15 is missing the word "a" in line 3, prior to the phrase "pharmaceutical composition."

### *Claim Rejections - 35 USC § 112, Second Paragraph*

14. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

15. The rejection of claims 1, 3, 4, 7-10, and 12-14 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant

regards as the invention because the phrase "in association with" is unclear, is maintained for the reasons of record.

Applicant argues that the term "in association with" is well understood. Applicant also argues that the timing of administration of the two components, at best, renders the claimed method overly broad, but not indefinite. Applicant's arguments have been considered, but they are not persuasive.

Applicant's dependent claims themselves provide evidence of why the phrase "in association with" is not only overly broad, but is also indefinite. Claim 9, for example, recites concomitant administration of amphotericin B and daclizumab. Claim 10, for example, recites administration with daclizumab, followed by a combination of amphotericin B and daclizumab. Claims 23 and 24 recite concomitant administration over a period of time in terms of weeks. Claim 30 recites administration in fourteen day cycles whereby the antibody drug is administered on the first day of each fourteen day cycle and a second, antifungal agent, to be administered on each day of the fourteen day cycle, with no apparent end to the limit of subsequent cycles. Because the independent claim 1 is not so limited in terms of time (i.e. in terms of days or weeks) when one or the other, or both agents are administered, nor is it so limited in terms of whether one agent should be administered first, second, or concomitantly, with or without repetition, the phrase "in association with" is unclear.

Additionally, Applicant's arguments appear to assert that the phrase "in association with" includes non-overlapping or separate administration of the two agents (see, e.g. Applicant's definition of the term "concomitantly" on page 8, paragraph 15 of the specification). For example, treatment with one agent could be separated by weeks or months before from treatment with the other. As previously stated in the Office Action of 8 June 2006, the phrase "in association with" does not reasonably apprise the skilled artisan of the metes and bounds of when the antifungal agent is to be administered in relation to administration of the IL-2Rp55 monoclonal antibody.

### *Claim Rejections - 35 USC § 102*

16. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

17. The rejection of claims 1, 3, 4, 7, and 8 under 35 U.S.C. 102(e) as being anticipated by Lai, US Patent 6,649,591 B2 (18 November 2003, publication date 18 April 2002, priority to 10 September 1996), is maintained for the reasons of record and the reasons set forth herein.

The claims recite a method for treating a human having a fungal infection, comprising intravenously administering to said patient a therapeutically effective amount of a polyene antifungal agent in association with a therapeutically effective amount of a chimeric or humanized monoclonal antibody that binds to the p55 subunit of the human IL-2 receptor that inhibits binding of IL-2 to an IL-2 receptor; wherein the monoclonal antibody is a humanized anti-Tac antibody; wherein the monoclonal antibody is daclizumab; wherein the polyene antifungal agent is amphotericin B; wherein the polyene antifungal agent is amphotericin B and the monoclonal antibody is daclizumab.

Applicant argues that claim 11 is free of the art and claim 11 has been combined with claim 1, thus the claims are free of the art. Applicant's argument has been fully considered, but is not persuasive.

Claim 1 has been amended to recite the limitations of treating a human comprising intravenously administering an effective amount of a polyene antifungal agent in combination with a therapeutically effective amount of a chimeric or humanized anti-CD25 monoclonal antibody. Lai teaches methods of treatment of subjects suffering from fungal infections (column 11, lines 10-13 and 31-32) with combinatorial therapeutic methods employing an effecting amount of a combination of at least one treating agent useful for the treatment of infections and/or inflammatory conditions and at least one dithiocarbamatie-containing nitric oxide scavenger (column 6, lines 35-44) wherein the expression of inducible nitric oxide synthase and overproduction of nitric oxide (column 14, lines 4-6) is associated with fungal infections (e.g. candidiosis and histoplasmosis) (column 14, lines 22-24). Lai teaches that treatment may be carried out with anti-cytokine antibodies (column 14, lines 48-50 and column 15, lines 13-19), antifungal therapeutics (column 14, line 62), including amphotericin B (column 17, lines 3-7), and anti-IL-2 monoclonal antibodies/IL-2 receptor antagonists, including daclizumab (column 17, lines 64-65; column 19, lines 62-63), anti-Tac(Fv)-PE40 monoclonal antibodies (column 19, lines 57-58), anti-CD25 monoclonal antibodies and anti-Tac antibodies (column 21, line 54). Lai teaches pharmaceutical formulations in the form of sterile injectable suspension (column 12, lines 66-67) and administration by intravenous delivery (column 26, lines 14-15). Lai et al., teaches intravenous administration and it is also well known in the art that both daclizumab and amphotericin B can be administered intravenously (see, for exemplary purposes only, Denning et al., Antimicrobial Agents and Chemotherapy. 1999 Nov; 43(11):2592-2599, especially at p. 2593, column 1, paragraph 5; and Pascual et al., Nephrol Dial Transplant. 2001 Sept; 16(9):1756-60, especially at p. 1756, column 2, second paragraph).

### *New Claim Rejections/Objections*

18. Claim 13 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 13 is dependent on claim 8, which is dependent on claim 1. Claim 13 recites intravenous administration of daclizumab, which is also recited in claim 1. As such, claim 13 fails to further limit claim 1.

### *Claim Rejections - 35 USC § 112, First Paragraph*

### *Scope of Enablement*

19. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

20. Claims 1, 3, 4, 7-10, 12-24, and 30-36 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating diagnosed or suspected aspergillosis, histoplasmosis, bastomycosis, coccidiomycosis, cryptococcosis, or candidaisis, in a human patient by intravenously administering a therapeutically effective amount of Amphotericin B concurrently with a therapeutically effective amount of daclizumab, does not reasonably provide enablement for a method of treating a generic fungal infection comprising intravenously administering a generic polyene antifungal agent in association with a therapeutically effective amount of a generic chimeric or humanized monoclonal antibody that binds to the p55 subunit of the human IL-2 receptor and inhibits binding of IL-2 to an IL-2R. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

The claims recite a method for treating a human having a fungal infection, comprising intravenously administering to said patient a therapeutically effective amount of a polyene antifungal agent in association with a therapeutically effective amount of a chimeric or humanized monoclonal antibody that binds to the p55 subunit of the human IL-2 receptor that inhibits binding of IL-2 to an IL-2 receptor; wherein the monoclonal antibody is a humanized anti-Tac antibody; wherein the monoclonal antibody is daclizumab; wherein the polyene antifungal agent is amphotericin B; wherein the polyene antifungal agent is amphotericin B and the monoclonal antibody is daclizumab; wherein administration of the therapeutically effective amount of amphotericin B and the therapeutically effective amount of daclizumab occurs concomitantly; wherein a part of the therapeutically effective amount of daclizumab is first administered followed by a combination of the remainder of the therapeutically effective amount of daclizumab in association with the therapeutically effective amount of amphotericin B; wherein the amount of amphotericin B is 0.3 to 25 mg/kg per day; wherein daclizumab is administered intravenously; wherein the amount of daclizumab is about 1 mg/kg one to four times per week; a method for treating a patient having a fungal infection, comprising administering over a given period of time to the patient (a) a first component consisting of pharmaceutical composition consisting of an injectable solution containing as an active ingredient an antimycotic agent in a therapeutically effective amount to decrease the severity of the fungal infection and (b) a second component consisting of an injectable solution containing as an active ingredient a chimeric or humanized monoclonal antibody that binds to the p55 subunit of the human interleukin-2 (IL-2) receptor and inhibits binding of IL-2 to an IL-2 receptor in a therapeutically effective amount to prevent reactions commonly experienced by patients who receive an antimycotic agent, said components being concomitantly administered over a period of time at least sufficient to resolve an invasive fungal infection; wherein the antimycotic agent is amphotericin B; wherein second component consists of an injectable solution containing as an active ingredient a humanized anti-Tac monoclonal antibody; wherein the anti-Tac monoclonal antibody is daclizumab; a method of treating a patient having a fungal infection, comprising concomitantly administering to the patient: (i) a first component consisting of an injectable solution containing as an active ingredient amphotericin B, and (ii) a second component consisting of an injectable solution containing as an active ingredient a chimeric or humanized monoclonal antibody that binds to the p55 subunit of the human interleukin-2 (IL-2) receptor and inhibits binding of IL-2 to an IL-2 receptor; wherein the active ingredient of the second component is a humanized anti-Tac antibody; wherein the active ingredient of the pharmaceutical composition of the first component is administered in an approximate amount of 0.3 to 25 mg per kg per day; wherein the active ingredient of the second component is administered in an approximate amount of 1 mg/kg to 2 mg/kg per week; wherein the components are concomitantly administered over a period of time from about 4 weeks to about 8 weeks; wherein the components are concomitantly administered over a period of time of about 8 weeks; a method for treating a patient having a fungal infection, comprising administering to the patient over a period of time at least sufficient to resolve an invasive fungal infection, in fourteen day cycles, (a) a first component, delivered on day 1 of each fourteen day cycle, consisting of an injectable solution containing as an active ingredient a chimeric or humanized monoclonal antibody that binds to the p55 subunit of the human interleukin-2 (IL-2) receptor and inhibits binding of IL-2 to an IL-2 receptor in a therapeutically effective amount to prevent reactions commonly experienced by patients who receive an antifungal agent, and (b) a second component, delivered each day of each fourteen day cycle, consisting of pharmaceutical composition consisting of an injectable solution containing as an active ingredient an antifungal agent in a therapeutically effective amount to decrease the severity of the fungal infection; wherein said antifungal agent is amphotericin B; wherein said monoclonal antibody is an anti-Tac antibody; wherein said anti-Tac antibody is daclizumab; wherein the monoclonal antibody is administered in an amount of about 1 mg/kg to about 2 mg/kg weekly; wherein the antimycotic agent is administered in an amount of about 0.3-25 mg/kg daily; wherein components (a) and (b) are administered for a period of about 4 to 8 weeks.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is undue include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability, 5) existence of working samples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The nature of the invention is drawn to a method of treating a human patient with a fungal infection by administering a polyene antifungal agent with a chimeric or humanized antibody against the p55 subunit of the human IL-2 receptor that inhibits binding of IL-2 to the IL-2 receptor.

The state of the art discloses that polyene antifungal agents have been known in the art for over 50 years. Amphotericin B was first discovered in 1955 and is still the gold standard in treating fungal infections in humans (Kleinberg. Int J Antimicrob Agents. 2006 Jun;27 Suppl 1:12-6. Epub 2006 May 16, especially at p. S12, column 1, first paragraph). Amphotericin B has a broad spectrum of anti-fungal activities and has shown efficacy in a wide variety of fungal infections (p. S12, column 1, last paragraph to column 2, first paragraph). However, in spite of the broad-spectrum of anti-fungal activity, the clinical use of Amphotericin B is limited by nephrotoxicity (p. S12, column 2, second paragraph and p. S13, column 1). In an attempt to reduce nephrotoxicity, efforts have been made to reformulate Amphotericin B by replacing sodium deoxycholate formulations with other phospholipids of cholesterol. As a result, there are several amphotericin B formulations that are commercially available, including ABLC (amphotericin B lipid complex – composed of amphotericin B complexed with dimyristolphosphatidylcholine and dimyristoyphosphatidylglycerol), ABCD (amphotericin B colloidal dispersion – formed from amphotericin B complexed with cholesteryl sulphate), and L-Amphotericin B (liposomal amphotericin B – composed of amphotericin B complexed with hydrogenated soy phosphatidylcholine, disteroyl, phosphatidylglycerol and cholesterol) (p. S12, column 2, second paragraph). Amphotericin B is widely used in patients receiving transplants and undergoing surgery (p. S13, second column, second paragraph). Amphotericin B has been used in a wide range of durations for therapy, from 0 to 12 weeks in many cases (p. S15, Figure 1). Additionally, not all fungal infections respond well to treatment with amphotericin B, particularly as a first-line agent, and in part because of its toxic side effects (p. S16, column 1, second paragraph). Amphotericin B is capable of irreversibly binding to ergosterol in fungal cytoplasmic membranes, thus increasing membrane permeability and cell death through the leakage of cell contents (see i.e. Hoesley et al., Clin Updates Fung Inf, 1999 Jun 2(2) p.1-6, cited in the Office Action of 8 June 2006, page 2, first full paragraph). However, this mechanism of action makes the drug very toxic to humans and other mammals because amphotericin B also binds mammalian cholesterol (see i.e. Cybulska et al., Acta Biochimica Polonica 2002 49(1):67-75, cited in the Office Action of 8 June 2006, especially p. 69, first column, second paragraph; p. 72, entire page to p. 74).

Monoclonal antibodies against the IL-2 receptor p55 subunit (also known as TAC) have been known in the art for the past 20 years (Yodoi et al., Princess Takamatsu Symp. 1988;19:73-86, Abstract Only; and Moreau et al., Eur J Immunology. 1987 Jul;17(7):929-35, Abstract Only). Daclizumab and basiliximab are engineered humanized IgG monoclonal antibodies to the interleukin-2 (IL-2) receptor p55 subunit, that are FDA approved to prevent acute rejection after renal transplantation (Berard et al., Pharmacotherapy. 1999 Oct;19(10):1127-37, Abstract only). The p55 (TAC) subunit on the IL-2 receptor is expressed by T cells participating in allograft rejection but not by resting T cells (Waldmann et al., Curr Opin Immunol. 1998 Oct;10(5):507-12, p. 507, abstract).

Lai (US Patent 6,649,591, 18 November 2003, publication date 18 April 2002, priority to 10 September 1996) teaches methods of treatment of subjects suffering from fungal infections (column 11, lines 10-13 and 31-32) with combinatorial therapeutic methods employing an effecting amount of a combination of at least one treating agent useful for the treatment of infections and/or inflammatory conditions and at least one dithiocarbamatie-containing nitric oxide scavenger (column 6, lines 35-44) wherein the expression of inducible nitric oxide synthase and overproduction of nitric oxide (column 14, lines 4-6) is associated with fungal infections (e.g. candidiosis and histoplasmosis) (column 14, lines 22-24). Lai teaches that treatment bay be carried out with anti-cytokine antibodies (column 14, lines 48-50 and column 15, lines 13-19), antifungal therapeutics (column 14, line 62), including amphotericin B (column 17, lines 3-7), and anti-IL-2 monoclonal antibodies/IL-2 receptor antagonists, including daclizumab (column 17, lines 64-65; column 19, lines 62-63), anti-Tac(Fv)-PE40 monoclonal antibodies (column 19, lines 57-58), anti-CD25 monoclonal antibodies and anti-Tac antibodies (column 21, line 54). Lai teaches pharmaceutical formulations in the form of sterile injectable suspension (column 12, lines 66-67) and administration by intravenous delivery (column 26, lines 14-15).

The level of skill of those in the art is high and is related to knowledge of treatment of disease using combinations of commercially available pharmaceuticals with known risks and side-effects. The level of skill in the art is also high because of the complex nature of treating fungal infections and the well-documented toxicity antifungal compounds such as amphotericin B (see i.e. Hoesley et al., Clin Updates Fung Inf, 1999 Jun 2(2) p.1-6, cited in the Office Action of 8 June 2006, especially p. 1, first paragraph; page 2, second to fourth paragraphs,).

There is one example in the specification of a method for treating fungal infections (see Example specification, pp. 21-28). The Example appears to be a treatment study protocol, but no data or results are provided. Although neither data nor working examples are required, they are considered helpful in determining the enabling aspects of the claimed invention. In this case, the working example provided in the specification cannot be relied upon because it proposes a study protocol, but does not encompass any results or data from the proposed study.

Applicants' claims are excessively broad due, in part, to the complex and diverse nature of treatment of fungal conditions. Although the specification is enabling for a method of treating diagnosed or suspected aspergillosis, histoplasmosis, bastomycosis, coccidiomycosis, cryptococcosis, or candidaisis, in a human patient by intravenously administering a therapeutically effective amount of Amphotericin B concurrently with a therapeutically effective amount of daclizumab, it does not reasonably provide enablement for a method of treating a generic fungal infection comprising intravenously administering a generic polyene antifungal agent in association with a therapeutically effective amount of a generic chimeric or humanized monoclonal antibody that binds to the p55 subunit of the human IL-2 receptor and inhibits binding of IL-2 to an IL-2R. The state of the art shows that not all fungal conditions will be successfully treated by either or both of the claimed therapeutic agents (see Kleinberg et al., p. S16, column 1, second paragraph). Because it is not known whether any particular combination of a generic polyene antifungal agent and a generic chimeric or humanized monoclonal antibody that binds to the p55 subunit of the human IL-2 receptor and inhibits binding of IL-2 to an IL-2R, will be effective in treating a generic human fungal infection, the claimed method, as written, is unpredictable. There is no data or other guidance in the specification such that one would be able to reasonably predict the outcome of treatment of a generic fungal infection with a generic polyene antifungal agent and a generic chimeric or humanized monoclonal antibody against the IL-2R p55 subunit. As such, it would require undue experimentation to test various treatment regimes in humans having generic fungal infections with a sufficient number of polyene antifungal agents concurrently or concomitantly (as defined by Applicant in paragraph 15 of the specification) with anti-IL2R p55 chimeric or humanized monoclonal antibodies.

Due to the large quantity of experimentation necessary to determine whether the claimed method of treating a generic fungal infection comprising intravenously administering a generic polyene antifungal agent in association with a therapeutically effective amount of a generic chimeric or humanized monoclonal antibody that binds to the p55 subunit of the human IL-2 receptor and inhibits binding of IL-2 to an IL-2R, the lack of direction/guidance presented in the specification regarding same, the absence of working examples directed to same, the complex nature of the invention given that animal cells and fungal cells are both eukaryotic and use the same mechanisms to synthesize proteins and nucleic acids, which makes fungal infections especially difficult to treat, the state of the prior art establishing that administration of amphotericin B presents serious toxicity concerns, and the breadth of the claims which encompass generic polyene antifungal agents, and generic anti-IL-2Rp55 chimeric or humanized monoclonal antibodies for use in treating generic fungal infections in humans, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

### *Claim Rejections - 35 USC § 112, Second Paragraph*

21. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

22. Claim 12 recites the limitation "the method of claim 11" in line 1. There is insufficient antecedent basis for this limitation in the claim. Claim 11 is a canceled claim. For the purposes of expediting prosecution, claim 12 is read as depending from claim 8.

23. Claims 30-36 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The phrase “a given period of time at least sufficient” is indefinite for failing to specify the metes and bounds of the time period for administration, which appears to be a critical component of the claims.

24. Claim 9 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The term “concomitant” is defined in the specification at p. 8, paragraph 15. Where applicant acts as his

or her own lexicographer to specifically define a term of a claim contrary to its ordinary meaning, the written description must clearly redefine the claim term and set forth the uncommon definition so as to put one reasonably skilled in the art on notice that the applicant intended to so redefine that claim term. *Process Control Corp. v. HydReclaim Corp.*, 190 F.3d 1350, 1357, 52 USPQ2d 1029, 1033 (Fed. Cir. 1999). The term "concomitant" in claim 9 is used by the claim to mean "administration within the same course of treatment", while the accepted meaning is "concurrently" (American Heritage Dictionary, 2000). The term is indefinite because the specification does not clearly redefine the term. Additionally, the last sentence of paragraph 15, which defines the term "concomitantly" in the specification, includes one agent being administered before or after the other. This would not be concurrent administration. This makes the term "concomitant" in the claims unclear, as to what is intended. I didn't see a definition of "in association with" in the specification.

### *Claim Rejections - 35 USC § 102*

25. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

26. Claims 1, 9, 13, 15-20, 30-33 are rejected under 35 U.S.C. 102(e) as being anticipated by Lai, US Patent 6,649,591 B2 (18 November 2003, publication date 18 April 2002, priority to 10 September 1996).

The claims recite a method for treating a human having a fungal infection, comprising intravenously administering to said patient a therapeutically effective amount of a polyene antifungal agent in association with a therapeutically effective amount of a chimeric or humanized monoclonal antibody that binds to the p55 subunit of the human IL-2 receptor that inhibits binding of IL-2 to an IL-2 receptor; wherein the monoclonal antibody is a humanized anti-Tac antibody; wherein the monoclonal antibody is daclizumab; wherein the polyene antifungal agent is amphotericin B; wherein the polyene antifungal agent is amphotericin B and the monoclonal antibody is daclizumab.

Lai teaches methods of treatment of subjects suffering from fungal infections (column 11, lines 10-13 and 31-32) with combinatorial therapeutic methods employing an effecting amount of a combination of at least one treating agent useful for the treatment of infections and/or inflammatory conditions and at least one dithiocarbamatie-containing nitric oxide scavenger (column 6, lines 35-44) wherein the expression of inducible nitric oxide synthase and overproduction of nitric oxide (column 14, lines 4-6) is associated with fungal infections (e.g. candidiosis and histoplasmosis) (column 14, lines 22-24). Lai teaches that treatment bay be carried out with anti-cytokine antibodies (column 14, lines 48-50 and column 15, lines 13-19), antifungal therapeutics (column 14, line 62), including amphotericin B (column 17, lines 3-7), and anti-IL-2 monoclonal antibodies/IL-2 receptor antagonists, including daclizumab (column 17, lines 64-65; column 19, lines 62-63), anti-Tac(Fv)-PE40 monoclonal antibodies (column 19, lines 57-58), anti-CD25 monoclonal antibodies and anti-Tac antibodies (column 21, line 54). Lai teaches pharmaceutical formulations in the form of sterile injectable suspension (column 12, lines 66-67) and administration by intravenous delivery (column 26, lines 14-15). Lai et al., teaches intravenous administration and it is also well known in the art that both daclizumab and amphotericin B can be administered intravenously (see, for exemplary purposes only, Denning et al., Antimicrobial Agents and Chemotherapy. 1999 Nov; 43(11):2592-2599, especially at p. 2593, column 1, paragraph 5; and Pascual et al., Nephrol Dial Transplant. 2001 Sept; 16(9):1756-60, especially at p. 1756, column 2, second paragraph). Administration of the compounds in conjunction is taught at column 21, line 52. Combination therapy is taught at column 25, line 57. Co-administration is taught at column 26, line 7.

### *Claim Rejections - 35 USC § 103*

27. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

28. The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

29. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

30. Claims 1, 3, 4, 7-10, 12-24, and 30-36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lai, US Patent 6,649,591 B2 (18 November 2003, publication date 18 April 2002, priority to 10 September 1996), in view of Denning et al., (Antimicrobial Agents and Chemotherapy. 1999 Nov; 43(11):2592-2599), and/or Stamler et al., (US Patent 6,057,367, 2 May 2000), and Pascual et al., (Nephrol Dial Transplant. 2001 Sept; 16(9):1756-60).

The claims recite a method for treating a human having a fungal infection, comprising intravenously administering to said patient a therapeutically effective amount of a polyene antifungal agent in association with a therapeutically effective amount of a chimeric or humanized monoclonal antibody that binds to the p55 subunit of the human IL-2 receptor that inhibits binding of IL-2 to an IL-2 receptor; wherein the monoclonal antibody is a humanized anti-Tac antibody; wherein the monoclonal antibody is daclizumab; wherein the polyene antifungal agent is amphotericin B; wherein the polyene antifungal agent is amphotericin B and the monoclonal antibody is daclizumab; wherein administration of the therapeutically effective amount of amphotericin B and the therapeutically effective amount of daclizumab occurs concomitantly; wherein a part of the therapeutically effective amount of daclizumab is first administered followed by a combination of the remainder of the therapeutically effective amount of daclizumab in association with the therapeutically effective amount of amphotericin B; wherein the amount of amphotericin B is 0.3 to 25 mg/kg per day; wherein daclizumab is administered intravenously; wherein the amount of daclizumab is about 1 mg/kg one to four times per week; a method for treating a patient having a fungal infection, comprising administering over a given period of time to the patient (a) a first component consisting of pharmaceutical composition consisting of an injectable solution containing as an active ingredient an antimycotic agent in a therapeutically effective amount to decrease the severity of the fungal infection and (b) a second component consisting of an injectable solution containing as an active ingredient a chimeric or humanized monoclonal antibody that binds to the p55 subunit of the human interleukin-2 (IL-2) receptor and inhibits binding of IL-2 to an IL-2 receptor in a therapeutically effective amount to prevent reactions commonly experienced by patients who receive an antimycotic agent, said components being concomitantly administered over a period of time at least sufficient to resolve an invasive fungal infection; wherein the antimycotic agent is amphotericin B; wherein second component consists of an injectable solution containing as an active ingredient a humanized anti-Tac monoclonal antibody; wherein the anti-Tac monoclonal antibody is daclizumab; a method of treating a patient having a fungal infection, comprising concomitantly administering to the patient: (i) a first component consisting of an injectable solution containing as an active ingredient amphotericin B, and (ii) a second component consisting of an injectable solution containing as an active ingredient a chimeric or humanized monoclonal antibody that binds to the p55 subunit of the human interleukin-2 (IL-2) receptor and inhibits binding of IL-2 to an IL-2 receptor; wherein the active ingredient of the second component is a humanized anti-Tac antibody; wherein the active ingredient of the pharmaceutical composition of the first component is administered in an approximate amount of 0.3 to 25 mg per kg per day; wherein the active ingredient of the second component is administered in an approximate amount of 1 mg/kg to 2 mg/kg per week; wherein the components are concomitantly administered over a period of time from about 4 weeks to about 8 weeks; wherein the components are concomitantly administered over a period of time of about 8 weeks; a method for treating a patient having a fungal infection, comprising administering to the patient over a period of time at least sufficient to resolve an invasive fungal infection, in fourteen day cycles, (a) a first component, delivered on day 1 of each fourteen day cycle, consisting of an injectable solution containing as an active ingredient a chimeric or humanized monoclonal antibody that binds to the p55 subunit of the human interleukin-2 (IL-2) receptor and inhibits binding of IL-2 to an IL-2 receptor in a therapeutically effective amount to prevent reactions commonly experienced by patients who receive an antifungal agent, and (b) a second component, delivered each day of each fourteen day cycle, consisting of pharmaceutical composition consisting of an injectable solution containing as an active ingredient an antifungal agent in a therapeutically effective amount to decrease the severity of the fungal infection; wherein said antifungal agent is amphotericin B; wherein said monoclonal antibody is an anti-Tac antibody; wherein said anti-Tac antibody is daclizumab; wherein the monoclonal antibody is administered in an amount of about 1 mg/kg to about 2 mg/kg weekly; wherein the antimycotic agent is administered in an amount of about 0.3-25 mg/kg daily; wherein components (a) and (b) are administered for a period of about 4 to 8 weeks.

Lai teaches methods of treatment of subjects suffering from fungal infections (column 11, lines 10-13 and 31-32) with combinatorial therapeutic methods employing an effecting amount of a combination of at least one treating agent useful for the treatment of infections and/or inflammatory conditions and at least one dithiocarbamatie-containing nitric oxide scavenger (column 6, lines 35-44) wherein the expression of inducible nitric oxide synthase and overproduction of nitric oxide (column 14, lines 4-6) is associated with fungal infections (e.g. candidiosis and histoplasmosis) (column 14, lines 22-24). Lai teaches that treatment bay be carried out with anti-cytokine antibodies (column 14, lines 48-50 and column 15, lines 13-19), antifungal therapeutics (column 14, line 62), including amphotericin B (column 17, lines 3-7), and anti-IL-2 monoclonal antibodies/IL-2 receptor antagonists, including daclizumab (column 17, lines 64-65; column 19, lines 62-63), anti-Tac(Fv)-PE40 monoclonal antibodies (column 19, lines 57-58), anti-CD25 monoclonal antibodies and anti-Tac antibodies (column 21, line 54). Lai teaches pharmaceutical formulations in the form of sterile injectable suspension (column 12, lines 66-67) and administration by intravenous delivery (column 26, lines 14-15). Administration of the compounds in conjunction is taught at column 21, line 52. Combination therapy is taught at column 25, line 57. Co-administration is taught at column 26, line 7. Lai does not teach specific dose ranges or timing of administration of amphotericin B or daclizumab.

Denning et al., teach dose range evaluations for amphotericin B. Recommended dosages at the limit of tolerability range from 0.8 to 1.5 mg/kg of body weight daily (p. 2592, column 1, first paragraph). Treatment for at least two weeks is taught at p. 2592, column 1, first paragraph.

Stamler et al., ('367 patent) teach intravenous administration of amphotericin B in a 30 year old man with a fungal infection at a dose of 1mg/day that is decreased to 0.5mg/day then NO-substituted amphotericin B at a dose of 0.5mg/day for a total dose of 1gm over a period of 10 weeks until the patient's symptoms fully resolve (column 45, Example XIV, lines 65-67 to column 46, lines 1-12)

Pascual et al., teach dose regimes of basilizimab and daclizumab. Five 1 mg/kg doses every 2 weeks are taught at p. 1757, column 2, paragraphs 3 and 4. A first dose of 2 mg/kg followed by four doses every two weeks at 1 mg/kg is taught at p. 1758, column 1, paragraph 3. A dose regime of 2 mg/kg followed by 1 mg/kg at days 7, 14, and 28 (about four weeks) is taught at p. 1758, column 1, paragraph 4. Intravenous administration is taught on page 1758, column 2, second full paragraph.

It would have been prima facie obvious to combine the teachings of Lai with the dosing regimes taught by Denning et al., or Stamler et al., ('367 patent), and Pascual et al., because the pharmaceutical compositions amphotericin B and daclizumab are old and well known in the art and their dosing ranges and optimization for therapeutic treatment have been well described in the literature. One of ordinary skill in the art would have reasonably expected success because one would have only needed to follow the dose optimization taught by Denning et al., and/or the '367 patent, and Pascual et al., to carry out the methods taught by Lai for the most effective dosing and administration timing regime. Additionally, one of skill in the art is capable of adjusting the dose regimes of Denning et al., and/or the '367 patent, and Pascual et al., in terms of amounts of drug or over a period of weeks because dose optimization is routine in the art.

### *Conclusion*

**NO CLAIM IS ALLOWED.**

**This action is non-final.**

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Cherie M. Woodward whose telephone number is (571) 272-3329. The examiner can normally be reached on Monday - Thursday 9:00am-7:30pm (EST).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached on (571) 272-0961. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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